REMARKS

A. Status of the Claims

Claims 1-6, 12-17, 21-23, 25-31, 33, 35-37, 39-46, 49-52, 56, 59, 61, and 63-64 were pending in the case at the time of the Office Action, with claims 3-5 having been withdrawn from the case as being directed to a non-elected invention. Claims 1, 2, 6, and 16 are amended in the Amendment set forth herein. Claims 7-11, 18-20, 24, 32, 34, 38, 41-45, 47-48, 53-55, 57-58, 60, 62, and 65-204 have been canceled without prejudice or disclaimer. New claim 205 has been added. Therefore, claims 1-2, 6, 12-17, 21-23, 25-31, 33, 35-37, 39-46, 49-52, 56, 59, 61, 63-64, and 205 are currently pending and under consideration.

Support for the new claim and amendments of the claims can be found generally throughout the specification, such as in the claims as originally filed. An example of support for the limitation "comprising 5 consecutive amino acids of SEQ ID NO:2" (claim 1) and "comprises 10 consecutive amino acids of SEQ ID NO:2" (claim 2) can be found on page 21, lines 6-12. An example of support for "wherein cell death is modulated in the cell" can be found on page 6, line 28 – page 7, line 6. Support for new claim 205 can be found on page 21, lines 6-7.

B. The Claim Objections Are Overcome

Claims 1 and 6 have been objected to for reciting non-elected subject matter in addition to the elected subject matter of Spi2A. Applicant notes that claims 1 and 6 as written make reference only to the elected subject matter. Applicant reserves the right to prosecute non-elected subject matter in a continuation or divisional application.

Claim 6 has been further objected to for not reciting sequence identifiers. In the amendment set forth herein, claim 6 has been amended to recite sequence identifiers.

C. The Indefiniteness Rejections Under 35 U.S.C. §112, Second Paragraph, Are Overcome

Claims 1-2, 12-17, 21-23, 25-31, 33, 35-37, 39-46, 49-52, 56, 59, 61, and 63-64 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for reciting the term "Spi2A" as the sole means of identifying the claimed molecule. The Action indicates that the rejection can be obviated by amending the claims to specifically identity Spi2A, such as with sequence identifiers.

D. The Enablement Rejection Under 35 U.S.C. §112, First Paragraph, Is Overcome

Claims 1, 29-31, 33, 35-37, 39-46, 49-52, 56, 59, 61, and 63-64 are rejected under 35 U.S.C. §112, first paragraph, because the specification is said to not reasonably provide enablement for an *in vivo* method of modulating cell death in a human comprising contacting the human with any Spi2A polypeptide. The Examiner notes that the specification is enabling for an *in vitro* method of modulating cell death in a cell with an Spi2A polypeptide. Applicant traverses this rejection.

1. *In vitro* Data

Applicants have set forth in detail results of *in vitro* studies demonstrating that Spi2A protects cells from apoptosis. Example 1 sets forth *in vitro* data showing that the induction of Spi2A by NF-κB protects cells from TNF-α mediated cell death, apoptosis, and the lysosomal pathway of cell death. See Examples (page 50, line 5 – page 61, line 21). Further, the working examples set forth *in vitro* data demonstrating that Spi2A protects cells from caspase-independent programmed cell death, mitochondrial pathways of programmed cell death, the lysosomal pathway of cell death, and cell death due to reactive oxygen species. See Example 2, page 61, line 23 – page 64, line 31. Further, the specification reports that Spi2A is up-regulated during the development of naïve to memory cells, and the upregulation of this gene correlated

with the differentiation of CTLs into memory cells, which suggested that the up-regulation of Spi2A in CTLs facilitates the escape of memory cell precursors from programmed cell death. Example 3, page 65, line 1 – page 87, line 22.

2. Correlation of *In vitro* Data with *In vivo* Data in the Specification

Contrary to the assertion of the Examiner, the specification is not silent as to a correlation between *in vitro* results and *in vivo* data. In particular, Applicant has conducted studies in the mouse demonstrating that Spi2A determines the level of antigen-specific CD8 cells after infection of the mouse with LCMV. Specification, page 89, line 17 – page 91, line 2. The specification sets forth data demonstrating that expression of Spi2A increased the percentage and absolute number of anti-LCMV CD8 cells in Spi2A mice in two independent experiments. Specification, page 91, lines 4- page 93, line 9, FIGS. 19-20, and Table 7. Furthermore, *in vivo* studies demonstrate that Spi2A affects the potency of recall responses to LCMV. Specification, page 93, line 11 – page 94, line 4. These findings are consistent with the *in vitro* studies because they establish that Spi2A has an effect on memory cell differentiation and the escape of memory cells from programmed cell death.

3. The LCMV Mouse is an Established Model for Disease in Humans

Furthermore, Applicant herein submits a Declaration of Dr. Raymond M. Welsh (Exhibit A; hereinafter the "Declaration") as evidence that the LCMV mouse is a model for disease in humans associated with immunopathology, such as infectious disease, septic shock, hepatic failure, inflammatory diseases, liver disease, vascular disease, cardiovascular disease, cancer, bone disease, emphysema, neurodegenerative disease, viral infections, AIDS, immune disorders such as autoimmune disease, muscular dystrophy, and arthritis in humans. Dr. Welsh is a skilled a skilled virologist and immunologist who understands the immunology of LCMV. Declaration, ¶3.

Dr. Welsh has declared that "[a] skilled immunologist with an ordinary understanding of immunology would have recognized, at the of the priority date of the Application, that LCMV infection in mice is a model for many human diseases associated with T cell-mediated immunopathology." Declaration, ¶6. Examples of such diseases include, but are not limited to, diseases associated with increased lysosomal permeability, diseases associated with autophagic cell death, diseases associated with cell death mediated by TNF-α, diseases associated with reactive oxygen species, and diseases associated with necrosis. *Id.* Specific examples of such diseases are set forth in the pending claims, and include infectious diseases, septic shock, hepatic failure, inflammatory diseases, liver disease, vascular disease, cardiovascular disease, cancer, bone disease, emphysema, neurodegenerative disease, viral infections, AIDS, immune disorders such as autoimmune disease, muscular dystrophy, and arthritis. *Id.* In support of his opinion regarding the LCMV mouse model, Dr. Welsh cites literature that would be familiar to one having an ordinary understanding of immunology and virology. Declaration, paragraph 7. He cites the following references:

Zinkernagel, Vaccine 20:1913-1917, 2002 (Exhibit 1): This reference indicates that infection of adult mice with LCMV causes a more or less severe T cell mediated immunopathology, and that the organ that is primarily infected by the virus then determines the immunopathological disease. Examples of such diseases include choriomeningitis, hepatitis, graft-versus-host disease, and AIDS. See, *e.g.*, page 1914.

Klenerman and Zinkernagel, Immunological Reviews 159:5- 16, 1997 (Exhibit 2): This reference establishes that the infectious model has been established for over

60 years, and that LCMV is a model for diseases of the meninges, liver, lymph nodes, and immunodeficiency states including HIV.

Borrow *et al.*, J. Virology, 69:1059-1070, 1995 (Exhibit 3): This reference addresses the virus-induced immunosuppression induced by LCMV, the role of virus tropism in determining pathogenicity, and the role of dendritic cells. Similarities of LCMV to HIV are discussed.

Ciurea *et al.*, Proc. Natl. Acad. Sci. USA, 96:11964-11969, 1999 (Exhibit 4): This paper discusses the persistence of LCMV at very low levels in the immune mouse, and compares the results to infections with viruses and bacteria:

Odermatt *et al.*, Proc. Natl. Acad. Sci. USA, 88:8252-8256, 1991 (Exhibit 5): This paper shows that LCMV-induced acquired immune suppression in mice is caused by $CD8^+$-T-cell-dependent elimination of macrophages/antigen-presenting cells (abstract), and discusses a comparison to HIV.

Khanolkar *et al.*, Immunol Res. 2002; 26(1-3):309-21 (Exhibit 6): This paper discusses the LCMV mouse as a model for viral disease, MHC disease, and tumors.

Hotchin J., Cold Spring Harbor Symp. Quant Biol. 27:479-99, 1962 (Exhibit 7) – Discusses LCMV infection as a model for human autoimmune disease:

Zinkernagel *et al.*, J Exp Med 1986; 164:1075-1092 (Exhibit 8) – This paper shows that LCMV can cause a "virus-triggered but T cell-mediated liver disease [that] resembles the pathophysiology of acute hepatitis B virus infections in man(11-

13), and may therefore serve as an animal model of its immunological pathogenesis." Abstract.

Kagi *et al.*, J. Exp. Med. 1996; May 1; 183(5):2143-52 (Exhibit 9) – This reference discusses the LCMV mouse as a model for diabetes.

Jaeckel *et al.*, Annals of the NY Acad Sci 958:7-25, 2002(Exhibit 10) – This paper reviews transgenic mouse models of diabetes where LCMV induces immunopathology (infiltration by lymphocytes, activation of antigen presenting cells, and expression of inflammatory cytokines) in transgenic strains of mice that express a viral "self-antigen." See abstract, and pages 17-19.

Ohashi *et al.*, J. Immunol. 1993 Jun 1; 150(11):5185-94 (Exhibit 11) – This reference teaches that the LCMV mouse as a model for hyperglycemia.

Evans *et al.*, J. Exp. Med. 1996 Dec 1; 184(6):2371-84 (Exhibit 12) –This study describes the LCMV mouse as a model for autoimmune disease.

Stellrecht-Broomhall, Viral Immunol. 1991 Winter; 4(4):269-80 (Exhibit 13) – This reference indicates that studies of LCMV infection in mice have shown it to be a 'Rosetta Stone' for [the] immunopathologist" and indicates that "the role of virus-specific cytotoxic T cells (19), as well as their H-2 restriction (41); the mechanisms of immune complex diseases (26); and the demonstration of the ability of viruses to distort cellular functions in the absence of cytotoxicity (25) have all emanated from the murine LCMV model." Page 269. This paper describes LCMV infection of C3H3B mice as a model for autoimmune hemolytic anemia. See page 278.

Zinkernagel *et al.*, Nature 1985 Aug 29-Sep 4; 316(6031):814-7 (Exhibit 14) – This reference sets forth that susceptibility to murine LCMV maps to class I MHC genes, and thus represents a model for MHC/disease associations. See, *e.g.*, abstract. Such MHC/disease associations are said to include "chronic diseases of autoimmune, immunopathological or cancerous nature." Page 817.

Ludewig *et al.*, J. Exp. Med. 2000 Mar 6; 191(5):795-804 (Exhibit 15) - Regarding LCMV infection in mice and cancer, this paper describes use of LCMV infection of RIP-GP mice implanted with MC-GP fibrosarcoma cells as a model for assessing efficacy of induction of anti-tumor immunity. See page 797.

Oldstone MB, Prog Med Virol. 1975;19:84-119 (Exhibit 16) – According to this review article, "[p]ersistent LCM viral infection of mice is the prototype experimental model for [the] study of V-Ab [viral – antiviral antibody] immune complex disease." Page 106. This reference describes similarity between the pathophysiology of LCMV and other diseases associated with immune complex deposition, including systemic lupus erythematosus and blood vessel disease such as vasculitis. Page 108-109.

Nansen and Thomsen, J. Immunol. 2001, 166:982-988 (Exhibit 17) – Regarding LCMV infection in mice as a model for septic shock, this references sets forth that "LPS is a major active agent in the pathogenesis of Gram-negative septic shock," and that "[a] shock-like state can be induced by a single injection of LPS into animals" and that "systemic infection of mice with the noncytopathogenic lymphocytic choriomeningitis virus (LCMV) sensitized mice to low amounts of LPS." Abstract and page 982.

Furthermore, Dr. Welsh reviews a publication of the inventors after the priority date of the present application, Nature Immunology, 5(9):919-926, 2004 (Exhibit 18 of the Declaration) that provides information which supports the findings set forth in the application that Spi2A is a protective factor for memory T cell development. Declaration, ¶10. The paper presents results of the studies showing that the gene encoding Spi2A is upregulated in memory cell precursors. Exhibit 18, abstract and pages 920-922. It was also found that Spi2A upregulation protected LCMV-specific memory progenitors from programmed cell death. Exhibit 18, abstract, and pages 922-924. Thus, Spi2A promotes the survival of cytotoxic T lymphocytes, allowing them to differentiate into memory CD8 T cells.

Dr. Welsh further declares that "the information set forth in the specification establishes that Spi2A plays a critical role as a protective factor that facilitates the differentiation of memory T-lymphocytes." Declaration, ¶11. The inventor's publication of Liu *et al.* (Exhibit 18 of Declaration) provides evidence supporting the benefit of Spi2A in inducing T-cell mediated immunity *in vivo*. *Id.*

Dr. Welsh concludes that "[i]n view of the information set forth in the specification pertaining to the protective role of Spi2A in facilitating the differentiation of memory T-lymphocytes and the state of the art pertaining to LCMV, it is my belief that a person of ordinary skill in my field would understand that Spi2A will be of benefit in abrogating immunopathology associated with LCMV infection." Declaration, ¶12. He further notes that "a person of ordinary skill in my field, when presented with the present specification, would be able to practice the invention as claimed without an undue amount of experimentation." *Id.* He concludes that "[i]n view of the information set forth in the specification pertaining to the role of Spi2A in the induction of T-cell mediated immunity and the protective effect of LCMV-specific memory

progenitors from programmed cell death, one of ordinary skill in the art would understand that Spi2A or Spi2A equivalents may be of benefit in the treatment of infectious disease, septic shock, hepatic failure, inflammatory diseases, liver disease, vascular disease, cardiovascular disease, cancer, bone disease, emphysema, neurodegenerative disease, viral infections, AIDS, immune disorders such as autoimmune disease, muscular dystrophy, and arthritis in humans, and that no undue experimentation would be required to practice the claimed invention." *Id.*

4. The Level of Skill of Those in the Art is High

Applicants note, as admitted by the Examiner, that the level of skill in the art is deemed to be very high.

5. Guidance in the Specification and Working Examples

In view of the information set forth above pertaining to the *in vitro* and *in vivo* data set forth in the specification, the substantial information known in the art regarding Spi2A and the LCMV mouse and a model for human disease, one of ordinary skill in the art, being highly skilled, would be able to practice the invention without undue experimentation. Furthermore, as noted above, the specification is not silent as to *in vivo* use, and the results set forth using the LCMV mouse provide detailed guidance as to the applicability of the present invention to the modulation of cell death in human subjects affected by disease as set forth in the claims.

6. Quantity of Experimentation

The Examiner argues that the fact that there is "no known cure or preventive regimen" for cancer as supporting that the quantity of experimentation to practice the claimed invention would be undue. Applicants note that the claims are not directed to a method of curing or preventing cancer. Office Action, page 7. Rather, the claims are directed to a method of modulating cell death. As set forth above, the instant specification provides substantial and detailed information regarding the effect of Spi2A of cell death and memory cell development.

Further, the specification provides detailed information regarding *in vivo* studies, and the state of the art pertaining to the LCMV mouse and disease therapy (e.g., cancer) such that a person of ordinary skill in the art, would is highly skilled as admitted by the Examiner, would be able to practice the invention as claimed without undue experimentation.

7. The State of the Prior Art

The Examiner argues that "while considerable research has gone into identifying the *in vitro* function of serpins, one of skill in the art would recognize that a considerable amount of *in vitro* empirical testing is required, with no a priori expectation of success being present, before serpin 2a, e.g., Spi2A can be considered useful for a disease state." Office Action, page 8. As an initial point, Applicant, citing numerous references pertaining to the state of the art pertaining to serpins, appears to concede that the state of the art pertaining to the *in vitro* effects of serpins is advanced. Applicant further notes that the invention is directed to understanding the *in vivo* effects of serpins. As set forth in the specification, and further detailed in the Liu *et al.* reference (Exhibit 18), the present inventors have found that Spi2A functions to promote memory cell survival and development. *In vivo* studies in the LCVM mouse set forth in the specification support this conclusion. The Examiner, making no mention whatsoever regarding the studies pertaining to LCMV mice in the specification, appears to have overlooked these studies. Further, as detailed in the Declaration of Dr. Welsh, the state of the art pertaining to LCMV infection in mice was highly advanced at the time of the priority date.

The Examiner argues that there is often a lack of correlation between *in vitro* and *in vivo* studies. Applicant notes, as discussed above, that in the present case, the results pertaining to the function of Spi2A *in vitro* have correlated with results in the LCMV mouse. Applicant notes that Gura, cited by the Examiner has supporting that the state of the art pertaining to cancer treatment is unpredictable, is a reference was published about 6 years before the priority date of

the present application. Gura, an old reference in a rapidly advancing field (oncology), is not representative of the state of the art at the time of the priority date.

8. Conclusion

In view of the foregoing, one of ordinary skill in the art would be able to practice the invention as claimed without undue experimentation. Therefore, it is requested that the rejection of claims 1, 29-31, 33, 35-37, 39-46, 49-52, 56, 59, 61, and 63-64 under 35 U.S.C. §112, first paragraph, should be withdrawn.

E. The Rejection Under 35 U.S.C. §102(b) Based on Hillman is Overcome

Claims 1, 6, 12, 14-15, 17, 21-23, 25-31, 33, 39-40, 49-52, 56, 59, 61, and 63-64 are rejected under 35 U.S.C. §102(b) as being anticipated by Hillman *et al.* (U.S. Patent 5,854,023; "Hillman"). Hillman is said to teach a method of treating infections, neoplastic disorders, and immune disorders in a subject that comprise administering an antagonist or a pharmaceutical comprising a SHH polypeptide, a polypeptide which is said to include at least 4 amino acid residues of MAGVGCCA. It is acknowledged that Hillman does not explicitly refer to SHH as a Spi2A polypeptide. Nevertheless, the Examiner argues that there is no manipulative difference between the claimed invention and Hillman. Applicant traverses.

Claim 1 recites "[a] method for modulating cell death in a cell comprising contacting said cell with a polypeptide comprising 5 consecutive amino acids of SEQ ID NO:2, wherein cell death is modulated in the cell. Hillman does not anticipate the claimed invention because it does not expressly or inherently disclose each limitation of the claimed invention. See *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."); see also *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) ("The identical

invention must be shown in as complete detail as is contained in the ... claim."). In particular, Hillman disclose any polypeptide comprising 5 consecutive amino acids of SEQ ID NO:2, nor any method for modulating cell death of a cell that involves contacting a cell with such a polypeptide, wherein cell death is modulated in the cell.

Regarding dependent claims, Hillman additionally does not anticipate claim 12 because it fails to disclose the limitation "wherein apoptosis of the cell is modulated." Applicant has reviewed Hillman and finds no such disclosure in Hillman. Although Hillman makes reference to treatment of cancer, it is silent as to whether any mechanism set forth therein results in modulation of apoptosis of any cell. Applicant notes that apoptosis is not the only mechanism of cell death in cancer. Other mechanisms include necrosis, autophagy, and nonlysosomal cell disintegration. Hillman is silent as to any of these mechanisms.

In view of the foregoing, Hillman fails to anticipate any of claims 1, 6, 12, 14-15, 17, 21-23, 25-31, 33, 39-40, 49-52, 56, 59, 61, and 63-64. Therefore, it is requested that this rejection should be withdrawn.

F. Conclusion

In view of the foregoing, each of the pending claims is in condition for allowance, and a Notice of Allowance is earnestly solicited.

The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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Date: January 24, 2007